EXHIBIT T

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/137,919	04/21/2023	CHRISTOPHER NOEL BARNES	P-340-US3/71TD-343864-US3	4361

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EXAMINER
DRAPER, LESLIE A ROYDS

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
09/27/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 18/137,919	Applicant(s) BARNES et al.	
	Examiner Leslie A Royds Draper	Art Unit 1629	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 21 April 2023.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-15 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-15 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 21Apr23.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Claims 1-15 are presented for examination.

Acknowledgement is made of Applicant's Track 1 Request for Prioritized Examination filed April 21, 2023, which was granted on June 7, 2023.

Acknowledgement is made of the present application as a continuation of U.S. Patent Application No. 17/953,036, filed September 26, 2022, which is a continuation of U.S. Patent Application No. 16/555,216, filed August 29, 2019, now U.S. Patent No. 11,484,531 B2, which claims benefit under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 62/724,805, filed August 30, 2018.

Information Disclosure Statement

Applicant's Information Disclosure Statement filed April 21, 2023 (seven pages total) has been received and entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08a, the Examiner has considered the cited references.

Priority

Acknowledgement is made of the present application as a continuation of U.S. Patent Application No. 17/953,036, filed September 26, 2022, which is a continuation of U.S. Patent Application No. 16/555,216, filed August 29, 2019, now U.S. Patent No. 11,484,531 B2, which claims benefit under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 62/724,805, filed August 30, 2018. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of 35 U.S.C. §112(a) or the first paragraph of pre-AIA 35 U.S.C. §112, except for the best mode requirement. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of prior-filed U.S. Provisional Patent Application No. 62/724,805, filed August 30, 2018, appears to provide adequate written support and/or enabling guidance as required under 35 U.S.C. §112(a) or the first paragraph of pre-AIA 35 U.S.C. §112 for the full scope of subject matter provided for in claims 1-15 presently under examination.

Accordingly, the effective filing date of claims 1-15 is August 30, 2018 (the filing date of the '805 provisional application).

The Examiner will revisit the issue of priority as necessary each time the claims are amended.

Claim Rejections - 35 USC § 112(d) (Pre-AIA Fourth Paragraph)

The following is a quotation of 35 U.S.C. 112(d):

> (d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

The following is a quotation of pre-AIA 35 U.S.C. 112, fourth paragraph:

> Subject to the following paragraph [i.e., the fifth paragraph of pre-AIA 35 U.S.C. 112], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

1. Claim 2 is rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends.

In claim 2, Applicant recites "wherein the low peak inspiratory flow rate is less than about 60 L/min", which fails to properly further limit the subject matter of independent claim 1 from which claim 2 depends. At p.5, l.12-14 of the as-filed specification, Applicant defines the term "low peak inspiratory flow rate" as "a peak inspiratory flow rate less than about 60 L/min". The recitation, therefore, in claim 1 that "the patient has a low peak inspiratory flow rate" implicitly defines a patient with peak inspiratory flow rate of less than about 60 L/min as defined in the underlying specification. Applicant's reiteration that the "low peak inspiratory flow rate is less than about 60 L/min" in dependent claim 2 fails to add any further

limitations to the method already defined in claim 1 and, thus, fails to constitute a proper dependent claim within the meaning of 35 U.S.C. §112(d) (pre-AIA fourth paragraph). Clarification is required.

Applicant may cancel the claim, amend the claim to place the claim in proper dependent form, rewrite the claim in independent form, or present a sufficient showing that the dependent claim complies with the statutory requirements.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis (i.e., changing from AIA to pre-AIA) for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

2. Claims 1-12 and 14-15 are rejected under 35 U.S.C. 103 as being unpatentable over Pudi et al. (“A 28-Day, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Nebulized Revefenacin in Patients with Chronic Obstructive Pulmonary Disease”, *Respiratory Research*, 2017; 18:182, Published Online November 2, 2017, cited by Applicant on the 04/21/23 IDS) in view of Mahler et

al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 04/21/23 IDS) and Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 04/21/23 IDS),

citing to Gold PM ("The 2007 GOLD Guidelines: A Comprehensive Care Framework", *Respiratory Care*, 2009; 54(8):1040-1049) as evidence.

Pudi et al. teaches an experimental study of 355 patients with moderate to severe COPD who were selected at screening for a post-ipratropium bromide ratio of FEV1/forced vital capacity of <0.7 and a forced expiratory volume in one second (FEV1) of 30-80% of the predicted normal value (abstract; col.2, para.2, p.2). Pudi et al. teaches that the subjects were administered once-daily treatments of a 3 mL inhalation solution of 44, 88, 175 or 350 μg revefenacin or placebo via standard PARI LC Sprint jet nebulizer for 28 days, and that the mean % predicted FEV1 of the study population was 43.6% (± 12.58), and that the mean % predicted FEV1 of the study population that received 175 μg revefenacin was 44.0% (± 11.76) (abstract; "Patients and Treatments", col.2, para.2-3, p.2; "Patients", col.2, para.5, p.3; Table 1, p.5). Pudi et al. teaches that revefenacin at doses of ≥ 88 μg led to significant improvements in bronchodilation as measured by mean difference in baseline to day 28 trough FEV1, and also reduced the average number of albuterol puffs per day by more than one puff per day (abstract; "Discussion", col.1, para.1, p.8). Pudi et al. teaches that revefenacin provides an effective once-daily long-acting muscarinic antagonist therapy for COPD patients who require or prefer a nebulized drug delivery option (abstract; "Discussion", col.1, para.2, p.10).

Pudi et al. differs from the instant claims only insofar as it does not explicitly teach that the COPD subject has a low peak inspiratory flow rate (PIFR) of less than about 60 L/min (claims 1-2), less than about 50 L/min (claim 3), or "about 20 L/min to less than about 60 L/min" (claim 7).

Mahler et al. teaches an experimental study of 20 COPD patients with PIFR[1] of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of 35 ± 11 (abstract; "Study Subjects", col.1, para.3, p.104; Table 2, p.106). Mahler et al. teaches that the experimental study compared the efficacy of arformoterol aerosol solution (15 μg/2 mL) via nebulizer with salmeterol dry powder (50 μg) administered via DISKUS inhaler, and observed that at 15 min following administration, improvements in FEV1, FVC and IC were significantly higher with nebulized arformoterol than with dry powder salmeterol, and that at 2 hr following administration, changes in FVC and IC, but not FEV1, were significantly higher with nebulized arformoterol than with dry powder salmeterol (abstract; col.2, para.2, p.105-col.2, para.2, p.106; Table 3, p.106). Mahler et al. teaches that, at peak effect (2 hr), volume responses were greater with arformoterol via nebulizer compared with dry powder salmeterol in COPD patients with PIFR of < 60 L/min (abstract). Mahler et al. teaches that patients with suboptimal PIFR may not be capable of completely inhaling a dry powder bronchodilator into their lower respiratory tract (as a deep, hard inhalation is required to overcome the internal resistance of a dry powder inhaler (DPI) to deaggregate the powder into fine particles) and suggests that nebulized aerosol arformoterol achieved deeper penetration into the lower respiratory tract (col.1, para.1, p.107-col.2, para.1, p.107). Mahler et al. teaches that bronchodilator therapy via nebulization should be considered in COPD patients with suboptimal PIFR against a particular DPI (abstract; col.1, para.3, p.108).

Quinn et al. teaches the administration of the long-acting muscarinic antagonist revefenacin in doses of 22, 44, 88, 175, 350 and 700 μg in 10 mM citrate buffer in normal saline at pH 5.0 to patients with moderate to severe COPD and % predicted FEV1 of 47.2% (± 12.4) once daily for 7 days using a PARI LC Sprint jet nebulizer (abstract; col.2, para.4, p.72; Table 1, p.74). Quinn et al. observed that revefenacin was effective to provide a rapid onset and sustained duration of bronchodilator effect (col.2, para.1, p.78).

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[1] At col.2, para.1, p.104, Mahler et al. teaches that PIFR was measured using the IN-CHECK DIAL device using the simulated internal resistance of the DISKUS dry powder inhaler, which meets Applicant's definition set forth at p.5, l.12-13 and p.5, l.18-24 of the as-filed specification, which defines "low peak inspiratory flow rate" as "less than about 60 L/min" and the PIFR of < about 60 L/min as being measured "against the simulated resistance of a DISKUS® device".

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in modifying Pudi's method of administering nebulized revefenacin solution to a COPD patient with % predicted FEV1 of less than about 50% who also exhibits a PIFR of less than about 60 L/min (claims 1-2), or less than about 50 L/min (claim 3) or between about 20 L/min to less than about 60 L/min (claim 7) because Mahler et al. teaches that COPD patients with suboptimal PIFR and % predicted FEV1 exhibited greater therapeutic benefit from nebulized bronchodilator therapy compared to other conventional forms of therapy, such as DPI. The skilled artisan would have been motivated to do so because Mahler et al. teaches that nebulized bronchodilator therapy achieved greater therapeutic effect in patients with suboptimal PIFR of < 60 L/min as a function of its ability to penetrate deeper into the lower respiratory tract. It would, therefore, have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify Pudi's method of administering nebulized revefenacin solution to a COPD patient with % predicted FEV1 of less than about 50% who also exhibits a PIFR of less than about 60 L/min (claims 1-2), less than about 50 L/min (claim 3) or between about 20 L/min to less than about 60 L/min (claim 7) to maximize bronchodilator effect in such COPD patient population, as suggested by Mahler's teachings.

A person of ordinary skill in the art before the effective filing date of the claimed invention would have also had a reasonable expectation of success in modifying Pudi's 175 μg/3 mL revefenacin solution as an aqueous revefenacin solution in normal saline with pH 5.0 for administration via nebulizer because Quinn et al. teaches an aqueous solution of revefenacin in normal saline with pH of 5.0 as a suitable formulation for administering revefenacin to COPD patients via nebulizer. The skilled artisan would have found it *prima facie* obvious to employ an aqueous revefenacin solution in normal saline with pH 5.0 for administration once daily to Pudi's COPD patient via nebulizer because Quinn et al. teaches that such aqueous solution of 175 μg revefenacin in normal saline with pH 5.0 solution was effective to provide rapid onset and sustained duration of bronchodilator effect when administered via nebulizer at a once daily frequency.

In claim 1, Applicant recites "[a] method for treating [COPD] in a patient" comprising (a) selecting a patient with % predicted FEV1 of < about 50%, and who has a low PIFR (defined at p.5, l.12-13 as "less

than about 60 L/min") and (b) administering an aqueous solution of revefenacin to the selected patient using a nebulizer.

In claim 2, Applicant reiterates that the patient has a PIFR of less than about 60 L/min.

In claim 3, Applicant further limits the PIFR to < about 50 L/min.

In claim 4, Applicant further limits the % predicted FEV1 to < about 40%.

In claim 5, Applicant further limits the % predicted FEV1 to < about 30%.

In claim 7, Applicant further limits the PIFR to about 20 L/min to < about 60 L/min, and % predicted FEV1 from about 20% to < about 50%.

Pudi et al. teaches that the COPD patients were selected for the study on the basis of their % predicted FEV1 being 30-80%, noting that the mean % predicted FEV1 of the selected subjects receiving 175 μg revefenacin in a 3 mL inhalation solution was 44% ± the standard deviation of 11.76, thus, circumscribing a range of 32.24-55.76%.

Mahler et al. teaches the use of nebulized bronchodilator therapy in COPD patients with PIFR of < 60 L/min (53.3 ± 5.0 L/min) to optimize penetration and therapeutic effect of the bronchodilator therapy in such subjects with suboptimal PIFR.

As established above, Quinn et al. provides teachings relevant to the *prima facie* obviousness of employing an aqueous solution of revefenacin in normal saline with pH 5.0 for the reasons above.

At p.5, l.11 of the as-filed specification, Applicant defines the term "about" as ± 10% of the recited value. As a result, Applicant's recitation of < about 50% in claim 1 constitutes a range of < 45-55%, < about 50 L/min in claim 3 constitutes a range of < 45-55 L/min, < about 40% in claim 4 constitutes a range of < 36-44%, and < about 30% in claim 5 constitutes a range of < 27-33%.

The teachings of Pudi et al. and Mahler et al. suggest the selection of COPD patients with a PIFR of less than 60 L/min (specifically, 53.3 ± 5.0 L/min, or a range of 48.3-58.3 L/min), and % predicted FEV1 of 32.24-55.76%, which clearly meet and/or overlap the ranges recited in instant claim 1 (i.e., < 45-55%), instant claim 3 (i.e., < 45-55 L/min) and instant claims 4-5 (i.e., < 36-44% in claim 4, or < 27-33% in claim 5). MPEP §2144.05 states, "In the case wherein the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191

USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) …" [A] prior art reference that discloses a range encompassing a somewhat narrower range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005)."

In claim 6, Applicant recites that the patient has severe to very severe COPD.

Gold is cited as factual evidence of the COPD classification known as the GOLD system, which characterizes COPD as mild, moderate, severe or very severe using FEV1: (i) FEV1 $\geq$ 80% (GOLD I, mild); (ii) 50% $\leq$ FEV1 < 80% (GOLD II, moderate); (iii) 30% $\leq$ FEV1 < 50% (GOLD III, severe), and (iv) FEV1 < 30% (GOLD IV, very severe) (Fig.1, p.1042).

In light of such art-accepted classification, Applicant's recitation that the patient has "severe to very severe COPD" is understood to constitute a subject with % predicted FEV1 of < 50%.

The teachings of Pudi et al. suggest the selection of COPD patients with a % predicted FEV1 of 44% $\pm$ 11.76, or a range of 32.24-55.76%, which circumscribes a % predicted FEV1 of < 50% implied by "severe to very severe COPD" as claimed, thereby meeting the limitations of Applicant's instant claim 6.

In claim 9, Applicant recites that the aqueous solution has a pH of about 4.5-5.5.

In claim 10, Applicant recites that the aqueous solution has a pH of about 4.8-5.2.

In claim 11, Applicant recites that the pharmaceutical composition comprising the aqueous solution is isotonic.

In claim 12, Applicant recites that the pharmaceutical composition comprising the aqueous solution further comprises sodium chloride, citric acid and sodium citrate.

In claim 14, Applicant recites that the aqueous solution is administered using a jet nebulizer.

In claim 15, Applicant recites that the aqueous solution is administered once daily.

Pudi et al. teaches once daily administration of the aqueous revefenacin solution with a jet nebulizer, and Quinn et al. provides teachings relevant to the *prima facie* obviousness of formulating the aqueous revefenacin solution of Pudi et al. with citrate buffer in normal (isotonic) saline and pH of 5.0, thereby meeting Applicant's instantly claimed requirements.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention.

3. Claim 13 is rejected under 35 U.S.C. 103 as being unpatentable over Pudi et al. ("A 28-Day, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Nebulized Revefenacin in Patients with Chronic Obstructive Pulmonary Disease", *Respiratory Research*, 2017; 18:182, Published Online November 2, 2017, cited by Applicant on the 04/21/23 IDS) in view of Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 04/21/23 IDS) and Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 04/21/23 IDS),

citing to Gold PM ("The 2007 GOLD Guidelines: A Comprehensive Care Framework", *Respiratory Care*, 2009; 54(8):1040-1049) as evidence,

further in view of Hirsh et al. (U.S. Patent Application Publication No. 2004/0045546 A1; 2004, cited by Applicant on the 04/21/23 IDS).

Pudi in view of Mahler and Quinn, as applied above to claims 1-12 and 14-15.

Pudi in view of Mahler and Quinn differ from the instant claim only insofar as they do not explicitly teach that the aqueous solution is also sterile (claim 13).

Hirsh et al. teaches a composition for reconstitution with sterile water or sterile saline solution prior to administration via nebulizer (p.4, para.[0027]). Hirsh et al. teaches that tonicity-adjusting agents are used to enhance the overall comfort to the patient upon administration of the reconstituted solution to the patient, further teaching that a preferred osmolality of the reconstituted inhalation solution is 275-305 mOsm/kg (p.4, para.[0027]). Hirsh et al. teaches that sterile isotonic saline solution is effectively used to achieve the desired tonicity of the reconstituted inhalation solution (p.4, para.[0027]).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in formulating the aqueous revefenacin solution in normal saline with pH 5.0 for use in Pudi's method of treating COPD patients as modified by Mahler et al. and Quinn et al. with sterile, isotonic saline because Hirsh et al. teaches the formulation of inhalation solutions for nebulization with sterile, isotonic saline. The skilled artisan would have been motivated to specifically employ sterile, isotonic saline for this purpose in view of the introduction of such solution directly into the lungs and the desire to minimize or eliminate contamination of such solution with microorganisms capable of causing infection. It would, therefore, have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to formulate the bronchodilating aqueous revefenacin solution with pH 5.0 as suggested by Quinn's teachings in sterile, isotonic saline to ensure sterility of the solution and to minimize or eliminate any contamination of such solution with infection-causing microorganisms, as suggested by Hirsh et al.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention.

4. Claims 1-7, 9-12 and 14-15 are rejected under 35 U.S.C. 103 as being unpatentable over Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 04/21/23 IDS) in view of Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 04/21/23 IDS),

citing to Gold PM ("The 2007 GOLD Guidelines: A Comprehensive Care Framework", *Respiratory Care*, 2009; 54(8):1040-1049) as evidence.

Mahler et al. teaches an experimental study of 20 COPD patients with PIFR[2] of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of 35 ± 11 (abstract; "Study Subjects", col.1, para.3, p.104; Table 2, p.106). Mahler et al. teaches that the experimental study compared the efficacy of arformoterol aerosol solution (15 μg/2 mL) via nebulizer with salmeterol dry powder (50 μg) administered via DISKUS inhaler, and observed that at 15 min following administration, improvements in FEV1, FVC and IC were significantly higher with nebulized arformoterol than with dry powder salmeterol, and that at 2 hr following administration, changes in FVC and IC, but not FEV1, were significantly higher with nebulized arformoterol than with dry powder salmeterol (abstract; col.2, para.2, p.105-col.2, para.2, p.106; Table 3, p.106). Mahler et al. teaches that, at peak effect (2 hr), volume responses were greater with arformoterol via nebulizer compared with dry powder salmeterol in COPD patients with PIFR of < 60 L/min (abstract). Mahler et al. teaches that patients with suboptimal PIFR may not be capable of completely inhaling a dry powder bronchodilator into their lower respiratory tract (as a deep, hard inhalation is required to overcome the internal resistance of a DPI to deaggregate the powder into fine particles) and suggests that nebulized aerosol arformoterol achieved deeper penetration into the lower respiratory tract (col.1, para.1, p.107-col.2, para.1, p.107). Mahler et al. teaches that bronchodilator therapy via nebulization should be considered in COPD patients with suboptimal PIFR against a particular DPI (abstract; col.1, para.3, p.108).

Mahler et al. differs from the instant claims only insofar as it teaches the nebulized bronchodilator therapy as the β-agonist arformoterol, not an aqueous solution of revefenacin (claim 1), particularly wherein the composition comprising the aqueous revefenacin solution has (i) a pH of about 4.5 to about 5.5 (claim 9) or about 4.8 to about 5.2 (claim 10), or (ii) further comprises sodium chloride, citric acid and sodium citrate (claim 12).

Quinn et al. teaches the administration of the long-acting muscarinic antagonist revefenacin in doses of 22, 44, 88, 175, 350 and 700 μg in 10 mM citrate buffer in normal saline at pH 5.0 to patients

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[2] At col.2, para.1, p.104, Mahler et al. teaches that PIFR was measured using the IN-CHECK DIAL device using the simulated internal resistance of the DISKUS dry powder inhaler, which meets Applicant's definition set forth at p.5, l.12-13 and p.5, l.18-24 of the as-filed specification, which defines "low peak inspiratory flow rate" as "less than about 60 L/min" and the PIFR of < about 60 L/min as being measured "against the simulated resistance of a DISKUS® device".

with moderate to severe COPD and % predicted FEV1 of 47.2% (± 12.4) once daily for 7 days using a PARI LC Sprint jet nebulizer (abstract; col.2, para.4, p.72; Table 1, p.74). Quinn et al. observed that revefenacin was effective to provide a rapid onset and sustained duration of bronchodilator effect (col.2, para.1, p.78).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in substituting an aqueous solution of the long-acting muscarinic antagonist revefenacin as the nebulized bronchodilator therapy for the β-agonist arformoterol used in Mahler's method for treating COPD patients because each was known in the art as an effective nebulized bronchodilator for the treatment of COPD, as evidenced by Quinn's teachings. The substitution, therefore, of an aqueous solution of revefenacin for the β-agonist arformoterol in Mahler's nebulized COPD therapy would have been *prima facie* obvious before the effective filing date of the claimed invention because each was known in the art at such time as an effective bronchodilator for treating COPD and, thus, would have been reasonably interchanged with one another in Mahler's method based upon this functional equivalency. "When a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." See *KSR International Co. v. Teleflex, Inc.*, 82 USPQ2d 1385 (U.S. 2007) at 1395-96, quoting *Sakraida v. AG Pro., Inc.*, 425 U.S. 273 (1976) and *In re Fout*, 675 F.2d 297, 301 (CCPA 1981) ("Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious").

In claim 1, Applicant recites "[a] method for treating [COPD] in a patient" comprising (a) selecting a patient with % predicted FEV1 of < about 50%, and who has a low peak inspiratory flow rate (defined at p.5, l.12-13 as "less than about 60 L/min") and (b) administering an aqueous solution of revefenacin to the selected patient using a nebulizer.

In claim 2, Applicant reiterates that the patient has a PIFR of less than about 60 L/min.

In claim 3, Applicant further limits the PIFR to < about 50 L/min.

In claim 4, Applicant further limits the % predicted FEV1 to < about 40%.

In claim 5, Applicant further limits the % predicted FEV1 to < about 30%.

In claim 7, Applicant further limits the PIFR to about 20 L/min to < about 60 L/min, and % predicted FEV1 from about 20% to < about 50%.

Mahler et al. clearly teaches the treatment of 20 COPD patients with PIFR of < 60 L/min (53.3 ± 5.0 L/min) (or about 20 L/min to < about 60 L/min, as in claim 7) and % predicted FEV1 of < about 50% (35 ± 11) (or about 20% to < about 50%, as in claim 7) with nebulized arformoterol solution, which was effective to improve lung function as measured by FEV1, FVC and IC.

Such teachings necessarily require a step of determining the patient's PIFR, determining the patient's % predicted FEV1, and selecting such patients with PIFR of < about 60 L/min (53.3 ± 5.0 L/min, or a range of 48.3-58.3 L/min) and % predicted FEV1 of < about 50% (35 ± 11%, or a range of 24-46%) for treatment with a nebulizer for administration of the bronchodilator arformoterol aerosol solution.

As established above, Quinn et al. provides teachings relevant to the *prima facie* obviousness of substituting an aqueous solution of revefenacin for the arformoterol solution used in Mahler et al. for the reasons set forth above.

At p.5, l.11 of the as-filed specification, Applicant defines the term "about" as ± 10% of the recited value. As a result, Applicant's recitation of < about 50 L/min in claim 3 constitutes a range of < 45-55 L/min, < about 40% in claim 4 constitutes a range of < 36-44%, and < about 30% in claim 5 constitutes a range of < 27-33%.

The teachings of Mahler et al. suggest the selection of COPD patients with a PIFR of 53.3 ± 5.0 L/min, or a range of 48.3-58.3 L/min, and % predicted FEV1 of 35 ± 11%, or a range of 24-46%, which clearly meet and/or overlap the ranges recited in instant claim 3 (i.e., < 45-55 L/min) and instant claims 4-5 (i.e., < 36-44% in claim 4, or < 27-33% in claim 5). MPEP §2144.05 states, "In the case wherein the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) ..." [A] prior art reference that discloses a range encompassing a somewhat narrower range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005)."

In claim 6, Applicant recites that the patient has severe to very severe COPD.

Gold is cited as factual evidence of the COPD classification known as the GOLD system, which characterizes COPD as mild, moderate, severe or very severe using FEV1: (i) FEV1 $\geq$ 80% (GOLD I, mild); (ii) 50% $\leq$ FEV1 < 80% (GOLD II, moderate); (iii) 30% $\leq$ FEV1 < 50% (GOLD III, severe), and (iv) FEV1 < 30% (GOLD IV, very severe) (Fig.1, p.1042).

In light of such art-accepted classification, Applicant's recitation that the patient has "severe to very severe COPD" is understood to constitute a subject with % predicted FEV1 of < 50%.

The teachings of Mahler et al. suggest the selection of COPD patients with a PIFR of 53.3 $\pm$ 5.0 L/min, and % predicted FEV1 of 35 $\pm$ 11%, or a range of 24-46%, which constitutes a % predicted FEV1 of < 50% as implied by "severe to very severe COPD" as claimed, thereby meeting the limitations of Applicant's instant claim 6.

In claim 9, Applicant recites that the aqueous solution has a pH of about 4.5-5.5.

In claim 10, Applicant recites that the aqueous solution has a pH of about 4.8-5.2.

In claim 11, Applicant recites that the pharmaceutical composition comprising the aqueous solution is isotonic.

In claim 12, Applicant recites that the pharmaceutical composition comprising the aqueous solution further comprises sodium chloride, citric acid and sodium citrate.

In claim 14, Applicant recites that the aqueous solution is administered using a jet nebulizer.

In claim 15, Applicant recites that the aqueous solution is administered once daily.

Quinn et al. teaches an aqueous solution of revefenacin for administration via PARI LC Sprint jet nebulizer to COPD patients, which contains citrate buffer in normal (isotonic) saline, with pH of 5.0, once daily for 7 days, thereby meeting Applicant's instantly claimed requirements.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention.

5. Claim 13 is rejected under 35 U.S.C. 103 as being unpatentable over Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have

Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 04/21/23 IDS) in view of Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 04/21/23 IDS),

citing to Gold PM ("The 2007 GOLD Guidelines: A Comprehensive Care Framework", *Respiratory Care*, 2009; 54(8):1040-1049) as evidence,

as applied above to claims 1-7, 9-12 and 14-15,

further in view of Hirsh et al. (U.S. Patent Application Publication No. 2004/0045546 A1; 2004, cited by Applicant on the 04/21/23 IDS).

Mahler in view of Quinn, as applied above to claims 1-7, 9-12 and 14-15.

Mahler in view of Quinn differ from the instant claim only insofar as they do not explicitly teach that the aqueous solution is also sterile (claim 13).

Hirsh et al. teaches a composition for reconstitution with sterile water or sterile saline solution prior to administration via nebulizer (p.4, para.[0027]). Hirsh et al. teaches that tonicity-adjusting agents are used to enhance the overall comfort to the patient upon administration of the reconstituted solution to the patient, further teaching that a preferred osmolality of the reconstituted inhalation solution is 275-305 mOsm/kg (p.4, para.[0027]). Hirsh et al. teaches that sterile isotonic saline solution is effectively used to achieve the desired tonicity of the reconstituted inhalation solution (p.4, para.[0027]).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in formulating Quinn's aqueous revefenacin solution in normal saline with pH 5.0 for use in Mahler's method of treating COPD patients with sterile, isotonic saline because Hirsh et al. teaches the formulation of inhalation solutions for nebulization with sterile, isotonic saline. The skilled artisan would have been motivated to specifically employ sterile, isotonic saline for this purpose in view of the introduction of such solution directly into the lungs and the desire to minimize or eliminate contamination of such solution with microorganisms capable of causing infection. It would,

therefore, have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to formulate Quinn's bronchodilating aqueous revefenacin solution with pH 5.0 in sterile, isotonic saline to ensure sterility of the solution and to minimize or eliminate any contamination of such solution with infection-causing microorganisms, as suggested by Hirsh et al.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention.

6. Claim 8 is rejected under 35 U.S.C. 103 as being unpatentable over Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 04/21/23 IDS) in view of Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 04/21/23 IDS),

citing to Gold PM ("The 2007 GOLD Guidelines: A Comprehensive Care Framework", *Respiratory Care*, 2009; 54(8):1040-1049) as evidence,

as applied above to claims 1-7, 9-12 and 14-15,

further in view of Pudi et al. ("A 28-Day, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Nebulized Revefenacin in Patients with Chronic Obstructive Pulmonary Disease", *Respiratory Research*, 2017; 18:182, Published Online November 2, 2017, cited by Applicant on the 04/21/23 IDS).

Mahler in view of Quinn, as applied above to claims 1-7, 9-12 and 14-15.

Mahler in view of Quinn differ from the instant claims only insofar as they do not explicitly teach that the composition comprising the aqueous solution of revefenacin comprises about 175 μg/3 mL of revefenacin (claim 8).

Pudi et al. teaches an experimental study of 355 patients with moderate to severe COPD and mean % predicted FEV1 of 44% administered once-daily treatments of a 3 mL inhalation solution of 44, 88, 175 or 350 μg revefenacin or placebo via standard PARI LC Sprint jet nebulizer for 28 days (abstract; "Patients and Treatments", col.2, para.2-3, p.2; "Patients", col.2, para.5, p.3). Pudi et al. teaches that revefenacin at doses of ≥ 88 μg led to significant improvements in bronchodilation as measured by mean difference in baseline to day 28 trough FEV1 ("Discussion", col.1, para.1, p.8).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in formulating Quinn's aqueous revefenacin nebulization solution to comprise 175 μg in 3 mL for treatment of COPD patients in Mahler's method because Pudi et al. teaches the administration of revefenacin in a 3 mL inhalation solution via jet nebulizer in dosage amounts of 88 μg or 175 μg for the treatment of patients with moderate to severe COPD. The skilled artisan would have been motivated to formulate Quinn's aqueous revefenacin nebulization solution to comprise 175 μg in 3 mL because Pudi et al. teaches that the administration of revefenacin solution via jet nebulizer in this dosage quantity was effective to provide significant improvements in bronchodilation of subjects with moderate to severe COPD (as evidenced by mean % predicted FEV1 of < 50%). It would, therefore, have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to formulate Quinn's aqueous revefenacin nebulization solution to comprise 175 μg in 3 mL for the effective treatment of COPD patients, as evidenced by Pudi's teachings.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention.

Double Patenting

Statutory Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the claims that are directed to the same invention so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

7. Claims 1-15 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 54-68 of copending U.S. Patent Application No. 17/953,036.

This is a provisional statutory double patenting rejection since the claims directed to the same invention have not in fact been patented.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/apply/applying-online/eterminal-disclaimer.

8. Claims 1-7, 9-12 and 14-15 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11, 16-19, 26-27 and 30 of U.S. Patent Application No. 18/137,922 in view of Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 04/21/23 IDS),

citing to Gold PM ("The 2007 GOLD Guidelines: A Comprehensive Care Framework", *Respiratory Care*, 2009; 54(8):1040-1049) as evidence.

'922 recites a method for selecting an inhalation delivery device to administer revefenacin (or a pharmaceutically acceptable salt thereof) to a COPD patient comprising selecting a nebulizer as the inhalation delivery device to administer revefenacin (or salt thereof) to the COPD patient, wherein the patient has a PIFR of less than about 60 L/min and a % predicted FEV1 of less than about 50% (copending claim 1). '922 further defines the COPD patient as having moderate to very severe COPD (copending claim 2), severe to very severe COPD (copending claim 3), or severe COPD (copending claim 4). '922 further defines the patient as having a PIFR of less than about 50 L/min (copending claim 5), less than about 40 L/min (copending claim 6) or less than about 30 L/min (copending claim 7), or a % predicted FEV1 of less than about 40% (copending claim 8) or less than about 30% (copending claim 9), or a PIFR of about 20 L/min to less than about 60 L/min with a % predicted FEV1 of from about 20% to less than about 50% (copending claim 10). '922 further recites a step of administering revefenacin (copending claim 11).

Gold is cited as factual evidence of the COPD classification known as the GOLD system, which characterizes COPD as mild, moderate, severe or very severe using FEV1: (i) FEV1 $\geq$ 80% (GOLD I, mild); (ii) 50% $\leq$ FEV1 < 80% (GOLD II, moderate); (iii) 30% $\leq$ FEV1 < 50% (GOLD III, severe), and (iv) FEV1 < 30% (GOLD IV, very severe) (Fig.1, p.1042).

The recitation, therefore, or moderate, severe or very severe COPD in the '922 claims is understood to define a % predicted FEV1 of 50% $\leq$ FEV1 < 80% (GOLD II, moderate), 30% $\leq$ FEV1 < 50% (GOLD III, severe), or FEV1 < 30% (GOLD IV, very severe), which establishes that the '922 copending claims 2-4 define a subject with % predicted FEV1 of less than about 50% as required by instant claim 1, as well as the "severe to very severe COPD" defined by instant claim 6.

'922 also recites a method for selecting an inhalation delivery device to administer revefenacin (or a pharmaceutically acceptable salt thereof) to a COPD patient comprising selecting a nebulizer as the inhalation delivery device to administer revefenacin (or salt thereof) to the COPD patient, wherein the patient has a % predicted FEV1 of less than about 50% and a PIFR of less than about 60 L/min, and

further wherein a DPI and metered dose inhaler does not deliver a therapeutically effective dose of a bronchodilator (copending claim 16). '922 recites the same method, but for the narrower limitation that the patient has a PIFR of less than about 50 L/min (copending claim 17), less than about 40 L/min (copending claim 18) or less than about 30 L/min (copending claim 19), or a PIFR of about 20 L/min to less than about 60 L/min and a % predicted FEV1 of from about 20% to less than about 50% (copending claim 22).

'922 further recites a method for treating COPD in a patient, wherein the patient has a PIFR of less than about 60 L/min and a % predicted FEV1 of less than about 50%, comprising selecting a nebulizer as the inhalation delivery device to administer revefenacin (or a pharmaceutically acceptable salt thereof) to the patient (copending claim 26). '922 further limits the patient to one with a PIFR of about 20 L/min to less than about 60 L/min and a % predicted FEV1 of from about 20% to less than about 50% (copending claim 27).

'922 further recites a method for selecting an inhalation delivery device to administer revefenacin (or a pharmaceutically acceptable salt thereof) to a COPD patient comprising selecting a nebulizer as the inhalation delivery device to administer revefenacin (or salt thereof) to the COPD patient, wherein the patient has a PIFR of about 20 L/min to less than about 60 L/min and a % predicted FEV1 of from about 20% to less than about 50% (copending claim 30).

In the '922 specification, the applicant defines the nebulizer as, e.g., a jet nebulizer (p.10, l.12-13), thereby establishing this specific form of nebulizer to be an embodiment circumscribed by the '922 claims as defined by the underlying disclosure.

'922 differs from the instant claims only insofar as it teaches only the selection of nebulized revefenacin for the COPD patient with the recited PIFR and % predicted FEV1 characteristics, but fails to explicitly recite the administration of revefenacin to this COPD patient as an aqueous solution (claim 1), particularly with pH of about 4.5 to about 5.5 (claim 9) or about 4.8 to about 5.2 (claim 10), or in which the aqueous solution further comprises sodium chloride, citric acid and sodium citrate (claim 12).

Quinn et al. teaches the administration of the long-acting muscarinic antagonist revefenacin in doses of 22, 44, 88, 175, 350 and 700 μg in 10 mM citrate buffer in normal saline at pH 5.0 to patients

with moderate to severe COPD and % predicted FEV1 of 47.2% (± 12.4) once daily for 7 days using a PARI LC Sprint jet nebulizer (abstract; col.2, para.4, p.72; Table 1, p.74). Quinn et al. observed that revefenacin was effective to provide a rapid onset and sustained duration of bronchodilator effect (col.2, para.1, p.78).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in modifying the '922 claims to further require a step of administering Quinn's aqueous revefenacin solution in normal saline with citrate buffer and pH 5.0 once daily to the COPD patient via the selected nebulizer because Quinn et al. teaches such aqueous solution as a suitable formulation for administration via nebulizer. The skilled artisan would have found it *prima facie* obvious to employ Quinn's aqueous revefenacin solution in normal saline with citrate buffer and pH 5.0 once daily to this COPD patient via the selected nebulizer because Quinn et al. teaches that such solution was effective to provide rapid onset and sustained duration of bronchodilator effect when administered via nebulizer at a once daily frequency.

In claim 9, Applicant recites that the aqueous solution has a pH of about 4.5-5.5.

In claim 10, Applicant recites that the aqueous solution has a pH of about 4.8-5.2.

In claim 11, Applicant recites that the pharmaceutical composition comprising the aqueous solution is isotonic.

In claim 12, Applicant recites that the pharmaceutical composition comprising the aqueous solution further comprises sodium chloride, citric acid and sodium citrate.

In claim 15, Applicant recites that the aqueous solution is administered once daily.

Quinn et al. teaches an aqueous solution of revefenacin for administration via jet nebulizer to COPD patients, which contains citrate buffer in normal (isotonic) saline with pH of 5.0, once daily, thereby meeting Applicant's instantly claimed requirements.

This is a provisional nonstatutory double patenting rejection.

9. Claim 13 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11, 16-19, 26-27 and 30 of U.S. Patent Application No. 18/137,922 in

view of Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 04/21/23 IDS),

citing to Gold PM ("The 2007 GOLD Guidelines: A Comprehensive Care Framework", *Respiratory Care*, 2009; 54(8):1040-1049) as evidence,

as applied above to claims 1-7, 9-12 and 14-15,

further in view of Hirsh et al. (U.S. Patent Application Publication No. 2004/0045546 A1; 2004, cited by Applicant on the 04/21/23 IDS).

'922 in view of Quinn, as applied above to claims 1-7, 9-12 and 14-15.

'922 in view of Quinn differ from the instant claim only insofar as they do not explicitly teach that the aqueous solution is also sterile (claim 13).

Hirsh et al. teaches a composition for reconstitution with sterile water or sterile saline solution prior to administration via nebulizer (p.4, para.[0027]). Hirsh et al. teaches that tonicity-adjusting agents are used to enhance the overall comfort to the patient upon administration of the reconstituted solution to the patient, further teaching that a preferred osmolality of the reconstituted inhalation solution is 275-305 mOsm/kg (p.4, para.[0027]). Hirsh et al. teaches that sterile isotonic saline solution is effectively used to achieve the desired tonicity of the reconstituted inhalation solution (p.4, para.[0027]).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in formulating Quinn's aqueous revefenacin solution in normal saline with citrate buffer and pH 5.0 for use in the '922 method of treating COPD patients as modified above with sterile, isotonic saline because Hirsh et al. teaches the formulation of inhalation solutions for nebulization with sterile, isotonic saline. The skilled artisan would have been motivated to specifically employ sterile, isotonic saline for this purpose in view of the introduction of such solution directly into the lungs and the desire to minimize or eliminate contamination of such solution with microorganisms capable of causing infection. It would, therefore, have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to formulate Quinn's

bronchodilating aqueous revefenacin solution with citrate buffer and pH 5.0 in sterile, isotonic saline to ensure sterility of the solution and to minimize or eliminate any contamination of such solution with infection-causing microorganisms, as suggested by Hirsh et al.

This is a provisional nonstatutory double patenting rejection.

10. Claim 8 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11, 16-19, 26-27 and 30 of U.S. Patent Application No. 18/137,922 in view of Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 04/21/23 IDS),

citing to Gold PM ("The 2007 GOLD Guidelines: A Comprehensive Care Framework", *Respiratory Care*, 2009; 54(8):1040-1049) as evidence,

as applied above to claims 1-7, 9-12 and 14-15,

further in view of Pudi et al. ("A 28-Day, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Nebulized Revefenacin in Patients with Chronic Obstructive Pulmonary Disease", *Respiratory Research*, 2017; 18:182, Published Online November 2, 2017, cited by Applicant on the 04/21/23 IDS).

'922 in view of Quinn, as applied above to claims 1-7, 9-12 and 14-15.

'922 in view of Quinn differ from the instant claim only insofar as they do not explicitly teach that the composition comprising the aqueous solution of revefenacin comprises about 175 μg/3 mL of revefenacin (claim 8).

Pudi et al. teaches an experimental study of 355 patients with moderate to severe COPD and mean % predicted FEV1 of 44% administered once-daily treatments of a 3 mL inhalation solution of 44, 88, 175 or 350 μg revefenacin or placebo via standard PARI LC Sprint jet nebulizer for 28 days (abstract; "Patients and Treatments", col.2, para.2-3, p.2; "Patients", col.2, para.5, p.3). Pudi et al. teaches that

revefenacin at doses of ≥ 88 μg led to significant improvements in bronchodilation as measured by mean difference in baseline to day 28 trough FEV1 ("Discussion", col.1, para.1, p.8).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in formulating the aqueous revefenacin nebulization solution to comprise 175 μg in 3 mL for treatment of COPD patients via nebulizer in the '922 method as modified by Quinn et al. because Pudi et al. teaches the administration of revefenacin in a 3 mL inhalation solution via jet nebulizer in dosage amounts of 88 μg or 175 μg for the treatment of patients with moderate to severe COPD. The skilled artisan would have been motivated to formulate the aqueous revefenacin nebulization solution to comprise 175 μg in 3 mL because Pudi et al. teaches that the administration of revefenacin solution via jet nebulizer in this dosage quantity was effective to provide significant improvements in bronchodilation of subjects with moderate to severe COPD (as evidenced by mean % predicted FEV1 of < 50%). It would, therefore, have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to formulate the aqueous revefenacin nebulization solution to comprise 175 μg in 3 mL for the effective treatment of COPD patients, as evidenced by Pudi's teachings.

This is a provisional nonstatutory double patenting rejection.

11. Claims 1-15 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 11,484,531 B2, citing to Gold PM ("The 2007 GOLD Guidelines: A Comprehensive Care Framework", *Respiratory Care*, 2009; 54(8):1040-1049) as evidence.

'531 recites a method for treating COPD in a patient comprising (a) selecting a patient having COPD for treatment based on the patient having a PIFR of less than about 60 L/min and a % predicted FEV1 of less than about 50%; and (b) administering a pharmaceutical composition comprising about 175 μg of revefenacin (or a pharmaceutically acceptable salt thereof) in 3 mL of an aqueous solution to the selected patient once daily using a nebulizer (patent claim 1). '531 further limits the patient to one with a PIFR of less than about 50 L/min (patent claim 2), % predicted FEV1 of less than about 40% (patent claim 3), or a PIFR of about 20 L/min to less than about 60 L/min and a % predicted FEV1 of about 20%

to less than about 50% (patent claim 4). '531 further defines the pharmaceutical composition as having a pH in the range of about 4.5 to about 5.5 (patent claim 5), or about 4.8 to about 5.2 (patent claim 6). '531 recites that the pharmaceutical composition is isotonic (patent claim 7), or sterile, isotonic and with pH of about 4.8 to about 5.2 (patent claim 9). '531 further recites that the pharmaceutical composition further comprises sodium chloride, citric acid, and sodium citrate (patent claim 8). '531 further defines the administration using a nebulizer as specifically employing a jet nebulizer (patent claim 10).

Gold is cited as factual evidence of the COPD classification known as the GOLD system, which characterizes COPD as mild, moderate, severe or very severe using FEV1: (i) FEV1 $\geq$ 80% (GOLD I, mild); (ii) 50% $\leq$ FEV1 < 80% (GOLD II, moderate); (iii) 30% $\leq$ FEV1 < 50% (GOLD III, severe), and (iv) FEV1 < 30% (GOLD IV, very severe) (Fig.1, p.1042).

As the '531 claims clearly provide for a COPD subject with a % predicted FEV1 of less than about 40% (patent claim 3), such COPD subject would be classified as having severe COPD per the art-accepted GOLD system classification, thereby necessarily meeting the requirements of instant claim 6.

In claim 1, Applicant requires that the patient exhibit "moderate to very severe COPD" and exhibit a % predicted FEV1 of less than about 50%.

As the '531 claims explicitly require the COPD patient to exhibit a % predicted FEV1 of less than about 50% as claimed, such patient of the '531 patent claims must also meet Applicant's preamble characterization in instant claim 1 of having "moderate to very severe COPD".

In claim 1, Applicant defines the patient as having "a low peak inspiratory flow rate".

At p.5, l.12-14 of the as-filed specification, Applicant defines the term "low peak inspiratory flow rate" as "a peak inspiratory flow rate less than about 60 L/min", which is clearly met by the method of the '531 patent claims that requires the patient to have at least a PIFR of less than about 60 L/min.

In claim 5, Applicant recites that the patient has a % predicted FEV1 of less than about 30%.

The '531 claims clearly describe a COPD patient with a % predicted FEV1 of less than about 40%, which circumscribes Applicant's range of less than about 30% as recited in instant claim 5 and, thus, renders such narrower range *prima facie* obvious in view of this clear overlap with the prior art. MPEP §2144.05 ("In the case where the claimed ranges 'overlap or lie inside ranges disclosed by the

prior art' a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) … "[A] prior art reference that discloses a range encompassing a somewhat narrower range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005)").

This is a nonprovisional nonstatutory double patenting rejection.

Conclusion

Rejection of claims 1-15 is proper.

No claims of the present application are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (M.P.E.P. §§ 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line (or paragraph) numbers (if available) in the as-filed specification, not the published application. Due to the procedure outlined in M.P.E.P. § 2163.06 for interpreting claims, other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is reminded that MPEP §2001.06(b) clearly states that "[t]he individuals covered by 37 C.F.R. 1.56 have a duty to bring to the attention of the examiner, or other Office official involved with the examination of a particular application, information within their knowledge as to other copending United States applications which are "material to patentability" of the application in question." See *Armour & Co. v. Swift & Co.*, 466 F.2d 767, 779, 175 USPQ 70, 79 (7th Cir. 1972). MPEP §2001.06(b) clearly indicates that "if a particular inventor has different applications pending in which similar subject matter but patentably indistinct claims are present that fact must be disclosed to the examiner of each of the involved applications." See *Dayco Prod. Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1365-69, 66 USPQ2d 1801, 1806-08 (Fed. Cir. 2003).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds Draper whose telephone number is (571)272-6096. The examiner can normally be reached Tuesday to Thursday (08:30 AM to 05:00 PM).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

September 22, 2023

Docket No.: 71TD-343864-US3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Theravance Biopharma R&D IP, LLC

Application No.: 18/137,919 Confirmation No.: 4361

Filed: April 21, 2023 Art Unit: 1629

For: Methods for Treating Chronic Obstructive Pulmonary Disease Examiner: Leslie A Royds Draper

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

INTRODUCTORY COMMENTS

This Reply is responsive to the Non-Final Office Action mailed September 27, 2023, concerning the above-referenced patent application. The Office set forth a three-month period to reply. As such, this Response is timely filed by its due date of December 27, 2023. In response to the Office Action, entry of the following amendments and consideration of the following remarks is respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

AMENDMENTS TO THE CLAIMS

1. (Original) A method for treating chronic obstructive pulmonary disease (COPD) in a patient with moderate to very severe COPD, the method comprising:

(a) selecting a patient having a percent predicted forced expiratory volume in one second less than about 50 percent; and

(b) administering a pharmaceutical composition comprising an aqueous solution of revefenacin or a pharmaceutically acceptable salt thereof to the selected patient using a nebulizer;

wherein the patient has a low peak inspiratory flow rate.

2. (Canceled)

3. (Original) The method of claim 1, wherein the low peak inspiratory flow rate is less than about 50 L/min.

4. (Original) The method of claim 1, wherein the patient has a percent predicted forced expiratory volume in one second less than about 40 percent.

5. (Original) The method of claim 1, wherein the patient has a percent predicted forced expiratory volume in one second less than about 30 percent.

6. (Original) The method of claim 1, wherein the patient has severe to very severe COPD.

7. (Original) The method of claim 1, wherein the patient has a peak inspiratory flow rate in the range of about 20 L/min to less than about 60 L/min and a percent predicted forced expiratory volume in one second in the range of from about 20 percent to less than about 50 percent.

8. (Original) The method of claim 1, wherein the pharmaceutical composition comprises about 175 µg/3 mL of revefenacin or a pharmaceutically acceptable salt thereof.

9. (Original) The method of claim 1, wherein the pharmaceutical composition has a pH in the range of about 4.5 to about 5.5.

10. (Original) The method of claim 1, wherein the pharmaceutical composition has a pH of about 4.8 to about 5.2.

11. (Original) The method of claim 1, wherein the pharmaceutical composition is isotonic.

12. (Original) The method of claim 1, wherein the pharmaceutical composition further comprises sodium chloride, citric acid and sodium citrate.

13. (Original) The method of claim 1, wherein the pharmaceutical composition is sterile, isotonic and has a pH of about 4.8 to about 5.2.

14. (Original) The method of claim 1, wherein the pharmaceutical composition is administered using a jet nebulizer.

15. (Original) The method of claim 1, wherein the pharmaceutical composition is administered once daily.

REMARKS

Applicant respectfully requests reconsideration of this application in view of the above amendments and following remarks.

Amendments to the Claims

By this paper, claim 2 is canceled without prejudice or disclaimer. No new matter is added by virtue of this amendment; thus, entry thereof is respectfully requested. Applicant reserves the right to pursue canceled subject matter in a continuing application.

This amendment adds, changes, and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Interview Summary

Applicant thanks Examiner Draper for the courtesies extended during the telephonic interview held on November 1, 2023, with the undersigned. The pending 35 U.S.C. §103 rejections were discussed, and the Examiner also noted the reply should address the remaining rejections. No agreement was reached.

Rejection under 35 U.S.C. § 112

Claim 2 is rejected under 35 U.S.C. §112(d) or 35 U.S.C. §112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends.

Without acquiescing to the rejection, but in a sincere attempt to expedite prosecution, claim 2 has been canceled, and Applicant respectfully requests withdrawal of the rejection.

Rejection under 35 U.S.C. § 103

Claims 1-12 and 14-15 are rejected under 35 U.S.C. §103 as being unpatentable over Pudi et al., "A 28-Day, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Nebulized

Revefenacin in Patients with Chronic Obstructive Pulmonary Disease," *Respiratory Research*, 2017; 18:182 (hereinafter "Pudi et al.")[1], in view of Mahler et al., "Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate," *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014, 27(2):103-109 (hereinafter "Mahler et al."), and Quinn et al., "Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies," *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79 (hereinafter "Quinn et al."), citing to "The 2007 GOLD Guidelines: A Comprehensive Care Framework," *Respiratory Care*, 2009; 54(8):1040-1049 (hereinafter "Gold PM") as evidence.

Claim 13 is rejected under 35 U.S.C. §103 as being unpatentable over Pudi et al. in view of Mahler et al. and Quinn et al. citing to Gold PM as evidence, further in view of U.S. Patent Publication No. 2004/0045546 A1 (hereinafter "Hirsh et al.").

Claims 1-7, 9-12, and 14-15 are rejected under 35 U.S.C. §103 as being unpatentable over Mahler et al. in view of Quinn et al., citing to Gold PM as evidence.

Claim 13 is rejected under 35 U.S.C. §103 as being unpatentable over Mahler et al. in view of Quinn et al., citing to Gold PM as evidence as applied above to claims 1-7, 9-12 and 14-15, further in view of Hirsh et al.

Claim 8 is rejected under 35 U.S.C. §103 as being unpatentable over Mahler et al. in view of Quinn et al., citing to Gold PM as evidence, as applied above to claims 1-7, 9-12, and 14-15, further in view of Pudi et al.

Applicant respectfully traverses for at least the following reasons.

---

[1] The Office alleges that "Pudi et al. differs from the instantly claims only insofar as it does not explicitly teach that the COPD subject has a low peak inspiratory flow rate (PIFR) of less than about 60 L/min." Office Action at p. 5. However, Applicant respectfully submits that, as acknowledged by the Office, "Pudi et al. teaches an experimental study of 355 patients . . . [having FEV1] of 30-80%." Office Action at p. 5. By contrast, the instant claims require that the selected patients have a percent predicted forced expiratory volume in one second less than about 50 percent.

Claim 1 is directed to a method for treating chronic obstructive pulmonary disease (COPD) in a patient with moderate to very severe COPD, the method comprising:

(a) selecting a patient having a percent predicted forced expiratory volume in one second less than about 50 percent; and

(b) administering a pharmaceutical composition comprising an aqueous solution of revefenacin or a pharmaceutically acceptable salt thereof to the selected patient using a nebulizer;

wherein the patient has a low peak inspiratory flow rate.

The present invention relates to unexpected results obtained by a clinical trial that studied the effect of bronchodilators delivered to COPD patients: specifically, revefenacin via a nebulizer versus tiotropium via dry powder. Data from a clinical study described in Example 1 of the instant application demonstrated that, "in subjects with more severe airflow limitation [percent predicted force expiratory volume in one second, FEV_1] <50% predicted), there were ***statistically significant and clinically relevant greater improvements in both trough FEV_1 and FVC for revefenacin administered using a nebulizer*** . . ." Lines 7-10, Page 15, instant application as filed. By contrast, "[i]n the intention-to-treat (ITT) population, . . . trends favoring revefenacin administered using a nebulizer over . . . a dry powder inhaler . . . did not meet statistical significance nor clinical relevance." Lines 4-7, Page 15, instant application as filed.

From this clinical study, contrary to expectations, it was discovered that peak inspiratory flow rate (PIFR) alone was not sufficient to predict which COPD patients will benefit from use of a nebulizer for delivery of a bronchodilator. *See* Example 1 and page 2 of the specification as filed. Further, prior to the clinical study by the Applicant, it was not expected and had not been demonstrated that COPD patients having ***low PIFR in combination with low FEV_1 (<50%)***—would gain an ***additional benefit*** from a bronchodilator (specifically, revefenacin) administered via a nebulizer as compared to COPD patients having ***low PIFR and $FEV_1 \geq 50$ %***. *See* Example 1 and page 2 of the specification as filed. Example 1 of the instant application demonstrates that following any alleged suggestions in any of the cited art (for selecting COPD patients with suboptimal PIFR for nebulized bronchodilator therapy) would not yield these therapeutically beneficial and

statistically significant effects on lung function as measured by FEV_1 and FVC when administered LAMA bronchodilator therapy.

Accordingly, prior to the advent of the claimed invention, Applicant submits that there was no reasonable expectation of success that ***selecting*** a patient having a percent predicted force expiratory volume in one second (FEV_1) less than about 50 percent, wherein the patient has low PIFR, and administering to such patients ***revefenacin*** using a ***nebulizer*** would achieve therapeutically beneficial effects. As there was no reasonable expectation of success, Applicant conducted the clinical trial described in Example 1.

For at least the foregoing reasons, Applicant submits that the art of record does not establish a *prima facie* case of obviousness and thus requests that the rejection be withdrawn.

Additionally, even if a *prima facie* case of obviousness were established, Applicant further submits that the clinical trial described in Example 1 demonstrates the unexpected difference in that the administration of nebulized LAMA revefenacin bronchodilator therapy yielded a significant change in FEV_1 in the claimed population of COPD subjects. For at least the foregoing reasons, Applicant respectfully submits that the present claims are not obvious and requests that the rejection be withdrawn.

Statutory Double Patenting

Claims 1-15 are provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 54-68 of copending U.S. Patent Application No. 17/953,036.

Applicant respectfully submits that a request for express abandonment under 37 C.F.R. 1.138 was filed on December 7, 2023, in U.S. Patent Application No. 17/953,036, and thus Applicant requests that the rejection be withdrawn.

Nonstatutory Double Patenting

Claims 1-7, 9-12, and 14-15 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11, 16-19, 26-27, and 30 of U.S. Patent Application No. 18/137,922 in view of Quinn et al., citing to Gold PM as evidence.

Claim 13 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11, 16-19, 26-27, and 30 of U.S. Patent Application No. 18/137,922 in view of Quinn et al., citing to Gold PM as evidence, as applied above to claims 1-7, 9-12, and 14-15, further in view of Hirsh et al.

Claim 8 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11, 16-19, 26-27 and 30 of U.S. Patent Application No. 18/137,922 in view of Quinn et al., citing to Gold PM as evidence, as applied above to claims 1-7, 9-12, and 14-15, further in view of Pudi et al.

Claims 1-15 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 11,484,531, citing to Gold PM as evidence.

Without acquiescing to the propriety of each of these rejections, and solely to expedite prosecution, Applicant submits herewith Terminal Disclaimers over U.S. Patent Application No. 18/137,922 and U.S. Patent No. 11,484,531, thereby rendering each rejection moot. Applicant requests that each of these obviousness-type double patenting rejections be withdrawn.

Applicant respectfully points out that the filing of a terminal disclaimer is not an admission of the propriety of the rejection. *See* M.P.E.P. § 804.02; *Quad Environmental Technologies Corp. v. Union Sanitary District*, 949 F.2d 870 (Fed. Cir. 1991).

CONCLUSION

In view of the above amendment, Applicant believes the pending application is in condition for allowance.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-4561. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 50-4561.

Dated: December 7, 2023

Respectfully submitted,

By /Joy Lynn Nemirow/
Joy Lynn Nemirow, Ph.D.
Registration No.: 67,163
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Attorney For Applicant

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NOTICE OF ALLOWANCE AND FEE(S) DUE

183577 7590 01/26/2024

Sheppard Mullin Richter & Hampton LLP/Theravance
650 Town Center Drive, 10th Floor
Costa Mesa, CA 92626

EXAMINER
DRAPER, LESLIE A ROYDS

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 01/26/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/137,919	04/21/2023	CHRISTOPHER NOEL BARNES	P-340-US3/71TD-343864-US3	4361

TITLE OF INVENTION: METHODS FOR TREATING CHRONIC OBSTRUCTIVE PULMONARY DISEASE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	04/26/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

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P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

183577 7590 01/26/2024
Sheppard Mullin Richter & Hampton LLP/Theravance
650 Town Center Drive, 10th Floor
Costa Mesa, CA 92626

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(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/137,919	04/21/2023	CHRISTOPHER NOEL BARNES	P-340-US3/71TD-343864-US3	4361

TITLE OF INVENTION: METHODS FOR TREATING CHRONIC OBSTRUCTIVE PULMONARY DISEASE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	04/26/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
DRAPER, LESLIE A ROYDS	1629	514-332000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

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❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (11/23) Approved for use through 03/31/2026 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/137,919	04/21/2023	CHRISTOPHER NOEL BARNES	P-340-US3/71TD 343864 US3	4361

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EXAMINER	
DRAPER, LESLIE A ROYDS	
ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 01/26/2024

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
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8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	**Application No.** 18/137,919	**Applicant(s)** BARNES et al.	
	Examiner Leslie A Royds Draper	**Art Unit** 1629	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the amendment submission dated 07 December 2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1 and 3-15 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 07Dec23.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☑ Other No drawings filed.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Applicant's Amendment filed December 7, 2023 has been entered into the present application.

Applicant's Information Disclosure Statement filed December 7, 2023 (one page total) has been received and entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08a, the Examiner has considered the cited references.

Claims 1 and 3-15 remain pending and under examination.

Claim 2 is cancelled.

EXAMINER'S STATEMENT OF REASONS FOR ALLOWANCE

For clarity of the record, Applicant is reminded that instant claims 1 and 3-15 are entitled to the benefit of the effective filing date of the earlier-filed U.S. Provisional Patent Application No. 62/724,805, filed August 30, 2018, as previously stated at p.3 of the September 27, 2023 non-final Office Action.

Applicant's claim 1 recites "[a] method for treating chronic obstructive pulmonary disease (COPD) in a patient with moderate to very severe COPD" via specifically selecting a patient having a percent predicted forced expiratory volume in one second (% predicted FEV1) of < about 50% and having a "low peak inspiratory flow rate" (defined at p.5, l.12-14 of the as-filed specification as "less than about 60 L/min"), and administering to this selected patient a pharmaceutical composition comprising an aqueous solution of revefenacin (or pharmaceutically acceptable salt thereof) via nebulizer (claim 1). Dependent claims 3-5 and 7 further limit the PIFR and/or % predicted FEV1 of the selected patient, dependent claim 6 further limits the severity of the COPD, and dependent claims 8-13 further limit the composition to require additional excipients and/or properties (e.g., pH). Dependent claim 14 specifies that the administration is performed via jet nebulizer, and dependent claim 15 specifies the frequency of administration of the pharmaceutical composition of revefenacin (i.e., "once daily"). Revefenacin was a known long-acting muscarinic antagonist bronchodilator effective for the treatment of COPD (Specification, p.6, l.27-32; Gerhart et al., U.S. Patent Application Publication No. 2016/0166506 A1, p.1, para.[0006], p.6, para.[0047], of record).

The closest prior art of record is Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, already of record) and Pudi et al. ("A 28-Day, Randomized, Double-Blind, Placebo-Controlled, Parallel Study of Nebulized Revefenacin in Patients with Chronic Obstructive Pulmonary Disease", *Respiratory Research*, 2017; 18:182, Published Online November 2, 2017, already of record).

Mahler et al. teaches an experimental study designed to determine "whether using a threshold of PIFRresist of <60 L/min against a specific DPI [dry powder inhaler] is a useful criterion for when to use a nebulizer to deliver bronchodilator medications", as DPI delivery may not achieve clinical benefit in patients unable to inhale a dry powder bronchodilator due to low PIFR (col.1, para.1, p.103; col.1, para.3, p.108). Mahler et al. teaches the selection of 20 COPD patients with PIFR of < 60 L/min (53.3 $\pm$ 5.0 L/min) to determine if lung function measured at 2 hr post-dose would be greater with a β-agonist bronchodilator delivered by nebulization than with inhalation from a DPI (col.1, para.2-3, p.104). Although not specifically selected on this basis, the 20 COPD subjects also exhibited a % predicted FEV1 of 35 $\pm$ 11 (Table 2, p.106). Mahler et al. reported that at peak effect (2 hr post-dose), volume responses as measured by forced vital capacity (FVC) and inspiratory capacity (IC) were significantly higher with nebulized arformoterol solution, as compared to salmeterol dry powder, with no significant change in FEV1 (abstract; Table 3, p.106). Mahler et al. concludes that "[b]ronchodilator therapy via nebulization should be considered in patients with COPD who have a suboptimal PIFRresist against a particular DPI" of <60 L/min (abstract). Mahler et al. did not specifically study the effects of long-acting muscarinic antagonist (LAMA) bronchodilator therapy in this population, and was limited to the specific selection of COPD patients based upon a low PIFR of < 60 L/min (not as coupled with % predicted FEV1).

Pudi et al. teaches an experimental study designed to "identify appropriate revefenacin doses for longer-term safety and efficacy trials" of 355 patients with moderate to severe COPD who were selected at screening for a post-ipratropium bromide ratio of FEV1/forced vital capacity of <0.7 and a forced expiratory volume in one second (FEV1) of 30-80% of the predicted normal value (abstract; col.1, para.3, p.2; col.2, para.2, p.2). Pudi et al. teaches that the subjects were administered once-daily treatments of a

3 mL inhalation solution of 44, 88, 175 or 350 μg revefenacin or placebo via standard PARI LC Sprint jet nebulizer for 28 days, and that the mean % predicted FEV1 of the study population was 43.6% (± 12.58), and that the mean % predicted FEV1 of the study population that received 175 μg revefenacin was 44.0% (± 11.76) (abstract; "Patients and Treatments", col.2, para.2-3, p.2; "Patients", col.2, para.5, p.3; Table 1, p.5). Pudi et al. teaches that revefenacin at doses of > 88 μg led to significant improvements in bronchodilation as measured by mean difference in baseline to day 28 trough FEV1, and also reduced the average number of albuterol puffs per day by more than one puff per day (abstract; "Discussion", col.1, para.1, p.8). Pudi et al. teaches that revefenacin provides an effective once-daily long-acting muscarinic antagonist therapy for COPD patients who require or prefer a nebulized drug delivery option (abstract; "Discussion", col.1, para.2, p.10). Pudi et al. did not specifically limit this moderate to severe COPD population to those with low PIFR of < 60 L/min, and also did not specifically select this moderate to severe COPD population using a % predicted FEV1 of < about 50% as claimed (as Pudi et al. allowed for a range of from 30-80%).

Applicant's working example of the as-filed specification presents an experimental study of LAMA bronchodilator therapy administered via nebulizer or DPI to COPD subjects with PIFR of <60 L/min (Ex.1, p.13, l.13-31). Applicant teaches that the 28-day study compared the effects of once-daily LAMA revefenacin (175 μg in 3 mL of an isotonic, sterile aqueous solution containing sodium chloride, citric acid, sodium citrate, and water for injection at pH 5.0) delivered via nebulizer, as compared to once-daily LAMA tiotropium (18 μg/day) via DPI, on lung function in these COPD patients with low PIFR (<60 L/min) after the 28-day administration period (Ex.1, p.13, l.13-30). Applicant observed that "there were trends favoring revefenacin administered using a nebulizer over tiotropium administered using a [DPI] for trough FEV1 and FVC, but such trends did not meet statistical significance nor clinical relevance" (Ex.1, p.15, l.4-7; Table 2, p.15; Tables 3-4, p.16). However, Applicant observed that "in subjects with more severe airflow limitation (FEV1 <50% predicted), there were statistically significant and clinically relevant greater improvements in both trough FEV1 and FVC for revefenacin administered using a nebulizer compared to tiotropium administered using a [DPI]", though "[n]o differences in trough IC were noted" (Ex.1, p.15, l.7-11; Table 2, p.15; Table 3-4, p.16).

Applicant's working example demonstrates that a comparison of LAMA bronchodilator therapy administered via DPI to LAMA bronchodilator therapy administered via nebulizer in COPD patients with suboptimal PIFR of <60 L/min does not provide statistically significant changes in lung function as measured by FEV1, FVC and IC, but a specific subpopulation of COPD patients with suboptimal PIFR of <60 L/min and % predicted FEV1 of <50% (which is the specific subpopulation recited in instant claim 1) did show statistically significant changes in lung function as determined by measures of obstruction (FEV1 and FVC) relevant to severity of COPD. Accordingly, Applicant's working example demonstrates that following the suggestion of Mahler's publication – i.e., selecting COPD patients with suboptimal PIFR of <60 L/min for nebulized bronchodilator therapy – would not yield these therapeutically beneficial and statistically significant effects on lung function as measured by FEV1 and FVC when administered the LAMA bronchodilator therapy revefenacin, as shown by Applicant's working example. Rather, Applicant demonstrates that it is the specific coupling of suboptimal PIFR of <60 L/min with % predicted FEV1 of <50% that yields these therapeutically beneficial and statistically significant effects on lung function as measured by FEV1 and FVC. Note that the working example properly compares the effects of LAMA bronchodilator therapy administered via nebulizer versus LAMA bronchodilator therapy administered via DPI, thereby comparing bronchodilators of like mechanism to determine the effect of administration route (nebulizer or DPI) on lung function in these specific COPD populations.

It is reiterated that Mahler's teachings, taken as a whole, specifically suggest the use of nebulized bronchodilator therapy versus DPI in COPD subjects with suboptimal PIFR <60 L/min, and makes no specific suggestions about particularly selecting COPD subjects for nebulized bronchodilator therapy that exhibit both suboptimal PIFR of <60 L/min *and* % predicted FEV1 of <50%. However, even if Mahler's teachings were interpreted as suggesting this population with PIFR <60 L/min and % predicted FEV1 of <50% (because the study subjects used therein exhibited % predicted FEV1 of 35 $\pm$ 11; Table 3, p.106), then at best the ordinarily skilled artisan would have reasonably expected that nebulized bronchodilator therapy would have yielded significant changes in FVC and IC, but not FEV1. Applicant, on the other hand, has demonstrated an unexpected difference in that the administration of nebulized LAMA revefenacin bronchodilator therapy did, in fact, yield a significant change in FEV1 in the claimed

population of COPD subjects. For these reasons, Applicant's claimed method is understood to patentably distinguish over this closest prior art of record.

Finally, Pudi's teachings fail to describe or suggest the selection of subjects with moderate to severe COPD that exhibit the specific features of low PIFR (< 60 L/min) and % predicted FEV1 of < about 50%. At best, Pudi et al. describes the selection of moderate to severe COPD patients with % predicted FEV1 of 30-80%, which coincides with the "moderate" to "severe" COPD classifications known in the art, as previously documented by Gold PM ("The 2007 GOLD Guidelines: A Comprehensive Care Framework", *Respiratory Care*, 2009; 54(8):1040-1049, already of record) and, thus, fails to teach the specific selection of this narrower subset of "moderate to very severe COPD" subjects with % predicted FEV1 of < about 50% (which includes a ± 10% variation, as defined by Applicant at p.5, l.11 of the as-filed specification, which is a range of < 55%) with suboptimal PIFR of < 60 L/min.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Claims 1 and 3-15 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds Draper whose telephone number is (571)272-6096. The examiner can normally be reached Tuesday to Thursday (08:30 AM to 05:00 PM).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

January 11, 2024